

PATENT SPECIFICATION

(11) 1227728

28
27
22
1

- NO DRAWINGS
 (21) Application No. 7176/69 (22) Filed 10 Feb. 1969
 (31) Convention Application No. 2117 (32) Filed 5 March 1968 in
 (33) Austria (OE)
 (45) Complete Specification published 7 April 1971
 (51) International Classification C 07 c 173/10
 (52) Index at acceptance

C2U 3 4A1 4A2 4X

(54) UNSATURATED AMINOSTEROIDS AND A PROCESS
FOR THE PREPARATION THEREOF

5

(71) We, OSTERREICHISCHE STICKSTOFFWERKE AKTIENGESELLSCHAFT, an Austrian Body Corporate of St. Peter 224, Linz/Donau, Austria, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

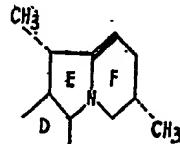
5

This invention relates to new unsaturated aminosteroids and to a process for the preparation thereof.

10

In our copending application No. 4757/69 (Serial No. 1226503) there are described and claimed new aminosteroids of the solanidine series which possess a double bond in the $\Delta 22/23$ position in the indolizidine ring system, in accordance with the partial formula:

10



15

It has now been found that these hitherto unknown amino-steroids on heating rearrange to give new compounds of the series which no longer possess the double bond in the F ring but in the E ring of the system and in particular in the $\Delta 20/22$ position. This thermal rearrangement surprisingly takes place without side-reactions or decomposition reactions in practically quantitative yield so that the process can be utilised without difficulty for preparative purposes. The $\Delta 20/22$ -unsaturated steroids thus obtained are very interesting since new routes are thereby opened up for degrading amino-steroids of the solanidine series by further reactions, preferably oxidation reactions, to nitrogen-free or nitrogen-containing steroids, especially C₂₁-steroids. Such derivatives are key products in the synthesis of many therapeutically valuable pharmaceuticals of the steroid series.

15

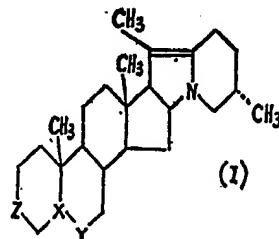
20

Accordingly the present invention provides an unsaturated aminosteroid having the general formula:

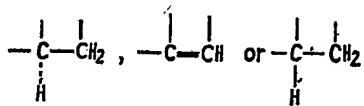
20

25

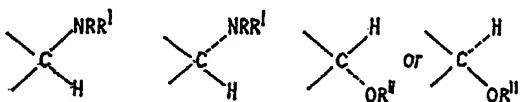
25



in which X—Y represents a group having the formula:



and Z represents a group having the formula =C=O, =C=NOH,

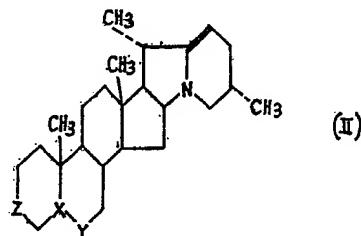


5 in which each of R and R', which may be the same or different, is a hydrogen atom or
an alkyl group and R'' is a hydrogen atom or an acyl group derived from an aliphatic,
araliphatic or aromatic carboxylic acid, and wherein in the case where Z represents
=C=O or =C=NOH and the group X—Y is saturated, there may be a double bond
between carbon atoms 4 and 5.

10 Examples of preferred compounds according to the present invention are: 10

5 α -solanid-20(22)-en-3 β -ol,
5,20(22)-solanidien-3 β -ol,
3 β -acetoxy-5 α -solanid-20(22)-ene,
3 β -acetoxy-5,20(22)-solanidiene,
15 5 α -solanid-20(22)-en-3-one,
5 β -solanid-20(22)-en-3-one,
solanid-4,20(22)-dien-3-one, and
3 β -dimethylamino-5 α -solanid-20(22)-ene 15

20 The present invention also provides a process for the preparation of an amino-
steroid of formula (I) herein which comprises heating, in the solid or fused state, a
 $\Delta_{22/23}$ -unsaturated aminosteroid having the general formula: 20



25 in which X—Y and Z have the same meaning as defined with respect to formula (I)
above.

The temperature at which the transformation is conducted is in itself not critical
if it is not significantly above 250°C. The actual temperature used determines the speed
of reaction so that the time of heating must be increased with decreasing temperature.
As a rule the temperature should be between 150°C. and 230°C. in order to ensure
acceptable reaction times and obtain pure products. Naturally the reaction temperature
also changes with the structure of the product employed.

30 The heat treatment can be effected by heating the solid product to a temperature
either below or above the melting point thereof. The reaction product can then be puri-
fied by subsequent sublimation or distillation.

35 It is particularly favourable to couple the rearrangement and purification by con-
tinuously removing the resulting $\Delta_{20,22}$ -compound from the reaction mixture. In the 35

case of heating to a temperature below the melting point this can be effected by continuous sublimation and in the case of heating to a temperature above the melting point by continuous distillation.

In order to assist the degree of purity of the product it is advisable to conduct the reaction under an atmosphere from which oxygen is largely excluded. This can be done by working either in vacuo or under an inert gas atmosphere, for example under a nitrogen atmosphere. The product thus obtained is then so pure, that further purification operations are not necessary.

The $\Delta_{22/23}$ -unsaturated aminosteroids of formula (II) which serve as the starting material may be obtained by treating the corresponding $\Delta_{22/N}$ -immonium salts with an alkaline reagent in the presence of a mixture of water and a water-miscible organic solvent, as described and claimed in our copending application No. 4757/69 (Serial No. 1226503). The $\Delta_{22/N}$ -immonium salt can be prepared by dehydrogenating the corresponding 22/N-saturated steroid, such as for example demissidine and solanidine, by treatment with a mercury salt and separating from the resulting isomer mixture the more sparingly soluble $\Delta_{22/N}$ -immonium salt from the more easily soluble $\Delta_{16/N}$ -immonium salt by fractional crystallisation from methanol.

The following Examples are given to illustrate the manner in which the process according to the invention may be carried into effect.

20

EXAMPLE 1

1 g of 5α -solanid-22(23)-en- 3β -ol is fused in a bulb tube at a vacuum of 10^{-2} mm Hg. by heating to 210°C . in an air bath. The 5α -solanid-20(22)-en- 3β -ol which forms as a result of the heat treatment is at the same time continuously distilled off. The distilled-off liquid solidifies in the receiver to give colourless crystals. After the distillation is complete the 5α -solanid-20(22)-en- 3β -ol is obtained in a yield of 95% of theory.

The product has the following physical characteristics:

Melting point: 197° to 199°C . $[\alpha]_D^{21} = +172^\circ$ (absolute diethyl ether)

$R_t = 0.63$ (benzene: methanol = 10:1, aluminium oxide G)

It has an IR-band at 1668 cm^{-1} .

The 5α -solanid-22(23)-en- 3β -ol serving as the starting material may be prepared by first reacting demissidine in acetic acid solution with mercuric acetate at the boiling point. The solid mercurous acetate is separated off and isolated and a mixture of isomeric immonium perchlorates is then precipitated from the filtrate by means of perchloric acid after removing the remnants of mercury salts with hydrogen sulphide. 5α -Solanid-22/N-en- 3β -ol perchlorate can be obtained from this mixture by fractional crystallisation from methanol, in the course of which it separates out in the first crystal fractions. On reacting the compound with sodium hydroxide in a 3:1 acetone-water mixture, 5α -solanid-22(23)-en- 3β -ol is obtained, having an R_t -value of 0.05 (benzene: methanol = 10:1, $\text{Al}_2\text{O}_3\text{G}$) which has a characteristic IR-band at 1663 cm^{-1} .

25

20

30

25

35

30

40

35

40

EXAMPLE 2

5 g. of 5α -solanid-22(23)-en- 3β -ol is fused in a vacuum distillation equipment by heating in an oil bath. The temperature is gradually raised from 220° to 250°C . in a vacuum of 8.10^{-3} mm. Hg. The product which has distilled off and which consists of crude 5α -solanid-20(22)-en- 3β -ol solidifies in the receiver to give a solid almost colourless mass of crystals.

Yield: 60% of theory.

Melting point: 185° to 189°C . $[\alpha]_D^{25} = +164^\circ$ (benzene)

$R_t = 0.60$ (benzene: methanol = 10:1, aluminium oxide G).

It possesses an IR-band at 1668 cm^{-1} .

45

45

50

50

EXAMPLE 3

1 g of 5α -solanid-22(23)-en- 3β -ol is fused in a vacuum distillation equipment by warming it to 195°C . in a heating bath. Before this, the air in the distillation equipment is displaced by nitrogen. The melt is maintained at 195°C . for 15 minutes whilst simultaneously passing nitrogen through the distillation equipment. Thereafter the temperature is raised to 205°C : and after discontinuing the flushing with nitrogen, the 5α -solanid-20(22)-en- 3β -ol is distilled off in a vacuum of 8.10^{-3} mm. Hg. The distillate immediately solidifies in the receiver to give a pale yellow-coloured crystal mass.

Melting point: 197° to 199°C . $[\alpha]_D^{21} = +172^\circ\text{C}$ (absolute diethyl ether)

$R_t = 0.63$ (benzene: methanol = 10:1, aluminium oxide G)

It possesses an IR-band at 1668 cm^{-1} .

55

55

60

60

EXAMPLE 4

2.0 g. of 5α -solanid-22(23)-en- 3β -ol dried to constant weight over phosphorus pentoxide is rearranged by heating in a vacuum sublimator dipping into a heating bath. For this purpose the heating bath is kept at a constant temperature of 185°C . The 5α -solanid-20(22)-en- 3β -ol which forms gradually sublimes off at a vacuum of 10^{-4} mm. Hg. As soon as the base employed has sublimed off apart from a minimal residue, the 5α -solanid-20(22)-en- 3β -ol is obtained in a yield of 93% of theory, in the form of needle-shaped colourless crystals.

Melting point: 197° to 199°C . $[\alpha]_D^{21} = +172^\circ$ (absolute diethyl ether)
 $R_t = 0.63$ (benzene:methanol=10:1, aluminium oxide G)

It possesses an IR-band at 1668 cm^{-1} .

EXAMPLE 5

10 g. of 5α -solanid-22(23)-en- 3β -ol is heated to 180°C in a vacuum sublimator in an oil bath. At the same time the apparatus is evacuated to 10^{-2} mm. Hg. and a moderate stream of hydrogen is passed into the sublimation apparatus. The 5α -solanid-20(22)-en- 3β -ol slowly sublimes off and deposits on the condensation surfaces in the form of colourless needles. After 5 hours 8.8 g. of a faintly pink-tinged sublimate are thus obtained, corresponding to a yield of 88% of theory.

Melting point: 197° to 199°C . $[\alpha]_D^{21} = +172^\circ$ (absolute diethyl ether)
 $R_t = 0.62$ (benzene:methanol=10:1, aluminium oxide G)

It possesses an IR-band at 1668 cm^{-1} .

EXAMPLE 6

100 g. of 5α -solanid-22(23)-en- 3β -ol are raised to 185°C . in a vacuum sublimator after displacing the air by hydrogen. As a result of the heat treatment 5α -solanid-20(22)-en- 3β -ol forms very rapidly and gradually sublimes off at a vacuum of 8.10^{-3} mm. Hg with the temperature being maintained at 185°C . Finally 92.7 g. of a colourless coarsely crystalline sublimate are obtained, corresponding to a yield of 92.7% of theory.

Melting point: 197° to 199°C . $[\alpha]_D^{21} = +172^\circ$ (absolute diethyl ether)
 $R_t = 0.63$ (benzene:methanol=10:1, aluminium oxide G)

It possesses an IR-band at 1668 cm^{-1} .

EXAMPLE 7

4.5 g. of $5,22(23)$ -solanidien- 3β -ol is distilled in a vacuum distillation equipment under a vacuum of 5.10^{-2} mm. Hg. The fine crystalline base is fused by heating to 175°C . On further heating of the heating bath up to 230°C . the $5,22(23)$ -solidien- 3β -ol is thermally converted to the $5,20(22)$ -solanidien- 3β -ol and the latter base is simultaneously purified by distillation. 4.35 g. of a colourless product which has solidified to crystals are thus obtained. The yield is thus 96.5% of theory.

Melting point: 198° to 204°C . $[\alpha]_D^{23} = +110^\circ$ (benzene)
 $R_t = 0.60$ (benzene:methanol=10:1, aluminium oxide G)

It possesses an IR-band at 1670 cm^{-1} .

The $5,22(23)$ -solanidien- 3β -ol can be obtained by following analogous procedure to that given in Example 1 for the preparation of 5α -solanid-22(23)-en- 3β -ol. It has an R_t value of 0.05 (benzene:methanol=10:1, aluminium oxide G):

EXAMPLE 8

350 mg. of $5,22(23)$ -solanidien- 3β -ol, dried to a constant weight over phosphorus pentoxide, is heated to 185°C . in a vacuum sublimator. The $5,20(22)$ -solanidien- 3β -ol sublimes off uniformly at a vacuum of 2.10^{-2} mm Hg. and with the temperature being kept constant. As soon as the $5,22(23)$ -solanidien- 3β -ol has been completely converted and sublimed off, 300 mg. of a fine crystalline sublimate of $5,20(22)$ -solanidien- 3β -ol is obtained.

Melting point: 202° to 204°C . $[\alpha]_D^{23} = +110^\circ$ (benzene)
 $R_t = 0.60$ (benzene:methanol=10:1, aluminium oxide G)

It possesses an IR-band at 1670 cm^{-1} .

EXAMPLE 9

In a manner analogous to that of Example 6, 46 g. of $5,22(23)$ -solanidien- 3β -ol yields 38.5 g. of $5,20(22)$ -solanidien- 3β -ol if the same reaction conditions are maintained.

Melting point: 202° to 206°C . $[\alpha]_D^{23} = +110^\circ$ (benzene)
 $R_t = 0.60$ (benzene:methanol=10:1, aluminium oxide G)

It possesses an IR-band at 1670 cm^{-1} .

EXAMPLE 10

1.7 g. of 3β -acetoxy- 5α -solanid-22(23)-ene is heated to 185°C . in a vacuum sublimator, from which the air had been displaced by hydrogen. On heating to 185°C . the 3β -acetoxy- 5α -solanid-22(23)-ene melts and thereby undergoes rearrangement to the 3β -acetoxy- 5α -solanid-20(22)-ene. The equipment is evacuated to 2.10^{-2} mm. Hg. and the 3β -acetoxy- 5α -solanid-20(22)-ene obtained by thermal conversion is distilled off. 1.45 g. of a pale yellowish-tinged distillate which has solidified to crystals and consists of 3β -acetoxy- 5α -solanid-20(22)-ene is obtained, corresponding to a yield of 85.3% of theory.

10 Melting point: 170° to 175°C . $[\alpha]_{D}^{20} = +120^\circ$ (benzene) 10
 $R_t = 0.84$ (benzene: methanol = 10:1, aluminium oxide G)
 It possesses an IR-band at 1673 cm^{-1} .

15 The 3β -acetoxy- 5α -solanid-22(23)-ene used as the starting material may be obtained by following an analogous procedure to that given in Example 1 for 5α -solanid-22(23)-en- 3β -ol, using a saturated sodium carbonate solution instead of sodium hydroxide for the rearrangement to the $\Delta 22(23)$ -compound. It has an R_t -value of 0.20 (benzene: methanol = 10:1, aluminium oxide G). 15

EXAMPLE 11

20 3.85 g. of 3β -acetoxy- 5α -solanid-22(23)-ene is heated to 170°C . in a vacuum sublimator, with the air being displaced by hydrogen beforehand. The conversion of the 3β -acetoxy- 5α -solanid-22(23)-ene to the 3β -acetoxy- 5α -solanid-20(22)-ene takes place as a result of the heat treatment. The equipment is evacuated to 2.10^{-2} mm. Hg. and the 3β -acetoxy- 5α -solanid-20(22)-ene is sublimed off and obtained in a yield of 87% of theory.

25 Melting point: 169°C . to 173°C . $[\alpha]_{D}^{20} = +125^\circ$ (benzene) 25
 $R_t = 0.84$ (benzene: methanol = 10:1, aluminium oxide G)
 It possesses an IR-band at 1673 cm^{-1} .

EXAMPLE 12

30 200 mg. of 3β -acetoxy- $5,22(23)$ -solanidiene is initially heated to 170°C . in a vacuum sublimator at a vacuum of 8.10^{-3} mm. Hg. On slowly raising the temperature to 185°C . the 3β -acetoxy- $5,20(22)$ -solanidiene formed sublimes off and is obtained as coarse crystals in a yield of 90% of theory.

35 Melting point: 184° to 186°C . $[\alpha]_{D}^{24} = +42.4^\circ$ (benzene) 35
 $R_t = 0.86$ (benzene: methanol = 10:1, aluminium oxide G)
 It possesses an IR-band at 1677 cm^{-1} .

40 The 3β -acetoxy- $5,22(23)$ -solanidiene which serves as the starting material may be prepared by following an analogous procedure to that given in Example 1 for 5α -solanid-22(23)-en- 3β -ol, using a saturated sodium carbonate solution instead of sodium hydroxide for the rearrangement to the $\Delta 22/23$ -compound. R_t -value = 0.20 (benzene: methanol = 10:1, aluminium oxide G). 40

EXAMPLE 13

45 265 mg. of 5α -solanid-22(23)-en-3-one is heated to 150°C . in a vacuum sublimator at a vacuum of 10^{-2} mm. Hg. by heating in an oil bath. As soon as material begins to sublime off the temperature of the oil bath is raised to 200°C . and the resulting 5α -solanid-20(22)-en-3-one is sublimed off as completely as possible and is obtained as a colourless crystalline sublimate in a yield of 91% of theory.

50 Melting point: 194° to 203°C . $[\alpha]_{D}^{23} = +165.8^\circ$ (benzene) 50
 $R_t = 0.88$ (benzene: methanol = 10:1, aluminium oxide GF)
 It possesses an IR-band at 1670 cm^{-1} .

EXAMPLE 14

55 200 mg. of 5β -solanid-22(23)-en-3-one is heated to 170° to 180°C in an oil bath at a vacuum of 10^{-2} mm. Hg. The 5β -solanid-20(22)-en-3-one which is thereby formed slowly sublimes off. It is obtained as a fine crystalline sublimate in a yield of 82.5% of theory.

55 Melting point: 180° to 183°C . $[\alpha]_{D}^{25} = +192.2^\circ$ (benzene) 55
 $R_t = 0.92$ (aluminium oxide GF, benzene: acetone: methanol = 7:3:2).
 It possesses an IR-band at 1673 cm^{-1} .

EXAMPLE 15

200 mg. of solani-4,22(23)-dien-3-one is heated to 180°C . in a vacuum sublimator

at 10^{-2} mm Hg. The solani-4,20(22)-dien-3-one sublimes off and deposits on the condenser as a fine crystalline sublimate in a yield of 85% of theory.

Melting point: 189° to 193°C. $[\alpha]_D^{25} = +190.4^\circ$ (benzene).

$R_t = 0.92$ (aluminium oxide GF, benzene:acetone:methanol = 7:3:2).

It possesses an IR-band at 1673 cm^{-1} .

5

5

EXAMPLE 16

250 mg. of 3β -dimethylamino- 5α -solanid-22(23)-ene is heated to 180°C. in a vacuum sublimator at 10^{-2} mm Hg. The 3β -dimethylamino- 5α -solanid-20(22)-ene thereby produced slowly sublimes off and deposits as a fine crystalline sublimate on the condenser. The yield is 60% of theory.

10

10

Melting point: 178° to 185°C. $[\alpha]_D^{25} = +127.4^\circ$ (benzene)

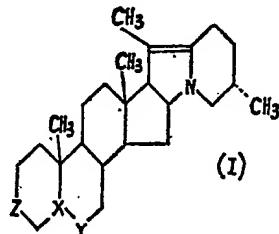
$R_t = 0.70$ (aluminium oxide GF, benzene:methanol = 10:1).

WHAT WE CLAIM IS:—

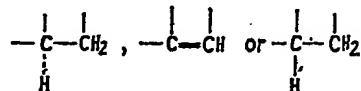
1. An unsaturated aminosteroid having the general formula:

15

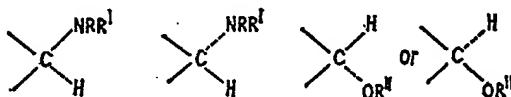
15



in which X—Y represents a group having the formula:



and Z represents a group having the formula $=\text{C}=\text{O}$, $=\text{C}=\text{NOH}$,



20 in which each of R and R', which may be the same or different, is a hydrogen atom or an alkyl group and R'' is a hydrogen atom or an acyl group derived from an aliphatic, araliphatic or aromatic carboxylic acid, and wherein, in the case where Z represents $=\text{C}=\text{O}$ or $=\text{C}=\text{NOH}$ and the group X—Y is saturated, there may be a double bond between carbon atoms 4 and 5.

25 2. 5α -Solanid-20(22)-en- 3β -ol.

3. $5,20(22)$ -Solanidien- 3β -ol.

4. 3β -Acetoxy- 5α -solanid-20(22)-ene.

5. 3β -Acetoxy- $5,20(22)$ -solanidiene.

6. 5α -Solanid-20(22)-en-3-one.

30 7. 5β -Solanid-20(22)-en-3-one.

8. Solani-4,20(22)-dien-3-one.

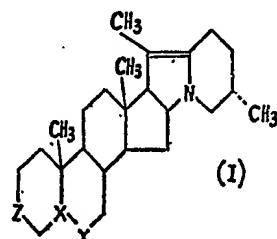
9. 3β -Dimethylamino- 5α -solanid-20(22)-ene.

20

25

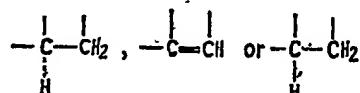
30

10. A process for the preparation of an unsaturated aminosteroid having the general formula:



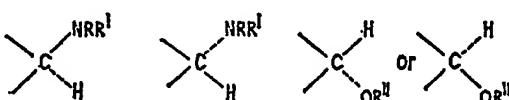
in which X—Y represents a group having the formula

5



5

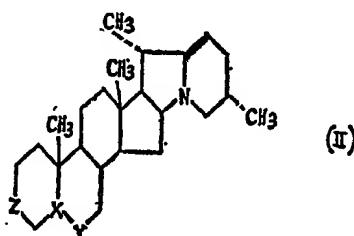
and Z represents a group having the formula =C=O, =C=NOH,



10

in which each of R and R', which may be the same or different, is a hydrogen atom or an alkyl group and R'' is a hydrogen atom or an acyl group derived from an aliphatic, araliphatic or aromatic carboxylic acid, and wherein, in the case where Z represents =C=O or =C=NOH and the group X—Y is saturated, there may be a double bond between carbon atoms 4 and 5, which comprises heating, in the solid or fused state, a $\Delta_{22/23}$ -unsaturated aminosteroid having the general formula:

10



15

in which X—Y and Z are as defined in Formula I above, and wherein, in the case where Z represents =C=O or =C=NOH and the group X—Y is saturated, there may be a double bond between carbon atoms 4 and 5.

15

11. A process according to claim 10, in which the temperature is maintained between 150° and 230°C.

20

12. A process according to claim 10 or 11, in which the compound of formula II is heated in the solid state and the reaction product is continuously sublimed off.

20

13. A process according to claim 10 or 11, in which the compound of formula II is heated in the fused state and the reaction product is continuously distilled off.

25

14. A process according to any one of claims 10 to 13, in which the heating is carried out under an atmosphere from which oxygen is largely excluded.

25

15. A process for the preparation of an unsaturated aminosteroid having the general

formula I herein substantially as hereinabove described with reference to the Examples.
16. Unsaturated aminosteroids of formula I herein whenever prepared by a process according to any one of claims 10 to 15.

STEVENS, HEWLETT & PERKINS,
Chartered Patent Agents,
Agents for the Applicants.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1971.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.